Ex. 3

NJD-440
Ellmann

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

JAN 11 1979

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Sidney M. Wolfe, M.D.
Mr. Benjamin Gordon
Public Citizen
Health Research Group
2000 P Street, N.W.
Washington, D.C. 20036

Dear Dr. Wolfe and Mr. Gordon:

Your letter of August 4, 1978, raised the question of talc carcinogenesis based on two letters submitted to the New England Journal of Medicine earlier this year. In particular, Dr. Marshall Deutsch stated that talc is closely related to the carcinogen asbestos and is likely to contain microscopic asbestos particles. Both talc and asbestos have been of concern to the Food and Drug Administration for several years, and we welcome this opportunity to discuss our continuous work in this area with you. We will preface our remarks, however, with some background material (Sections 1-2).

1. References Cited

The references cited in your letter are useful only because they raise an issue that deserves consideration on its own merits. The references themselves, however, are merely personal letters to the editor; their claims are neither scientifically controlled studies by the authors nor reviewed by peers. Indeed the letter of Moorehead and Oei merely refers to the one by Deutsch, who in turn quotes from a paragraph in Clinical Chemistry 22(7):1141, 1976, about an oral presentation to be given by K. Griffiths. This paragraph speaks only about "electron microscopic microanalysis" for identification in tissue of "contaminating particles such as asbestos or talc. . . ."

Dr. Deutsch's assertion that asbestos particles found on surgically removed ovaries could have migrated from talc used to dust condoms is unsupported speculation. He further asserts that Japanese men have more stomach cancer than men in other countries because they ingest rice dusted "with a mixture of talc and glucose." He gives no reference, but presumably has in mind "Talc-Treated Rice and Japanese Stomach Cancer," by R.R. Merliss, Science 173:1141-42, 1971. The facts, however, are that most Japanese eat unpolished rice; only the affluent can afford

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polished rice coated with glucose and talc. Furthermore, persons of Japanese ancestry in Hawaii and California, who do eat polished, coated rice, have a lower incidence of stomach cancer than the native Japanese! Apparently, the native Japanese are affected by many other environmental factors that could cause stomach cancer (see Haenszel, W., M. Kurihara, M. Segi and R.K.C. Lee, "Stomach Cancer among Japanese in Hawaii," Journal of the National Cancer Institute 49(4):969-988, October 1972).

Finally, Moorehead and Oei allege that FDA regulations discourage the replacement of talc in older drugs. The extent of testing to assure the adequacy of the reformulated products depends upon the drug itself. Currently, the replacement of talc with an acceptable excipient would not change its drug status; that is, new drug applications would not be required for "old" drugs. Although new drugs would require a supplemental application, the firm may still market its currently approved formulation while its application is pending. The FDA-sanctioned hardships alleged by Moorehead and Oei appear to be without foundation.

2. Asbestos versus Talc

Talc is a naturally occurring hydrous magnesium silicate similar in chemical composition to various asbestos minerals. However, unlike the fibrous forms of asbestos, talc normally exists as tabular or platy forms (attachment A). Indeed most asbestiform minerals also exist in non-fibrous forms. (See Dr. Ampian's article in attachment B.) Thus talc and asbestos are not similar in morphology. As you know, such experts as Mearl F. Stanton (NIH/National Cancer Institute) contend, on the basis of several studies, that it is not the chemical nature of asbestos as much as its physical configuration--long thin fibers--which make it carcinogenic (attachment C). There is to date no conclusive evidence that pure talc is carcinogenic in man or animals (attachment D). The FDA Asbestos Work Group and the OTC Panel on Antiperspirant Drug Products have reviewed the voluminous literature on talc and have independently determined that the evidence implicates asbestos contamination of talc as the offending exposure in "talc" carcinogenesis.

Industry awareness of our concern has led to improvement in the mining and processing of talc to minimize asbestos contamination. In 1973, the FDA published a proposed rule to prohibit the use of talc contaminated at the 0.1 percent level with asbestos in foods and drugs (38 FR 27076, September 28, 1973, attachment E). Implementation of this rule has been necessarily delayed until an appropriately sensitive method for regulatory purposes could be

developed (40 FR 11865, March 14, 1975, attachment F). In cooperation with scientists from industry, our scientists have been making progress in the development of such regulatory methods (attachment B).

Meanwhile, the FDA Bureau of Foods has carried out several x-ray powder diffraction surveys of the asbestos contamination of cosmetic talc (talcum powders). They found that cosmetic grades of talc are usually free of asbestiform particles. For example, in a 1977 investigation of 46 talc samples, the FDA found only three to contain asbestos (tremolite or anthophyllite; see attachment E) and even then the level was only 0.1 percent or less. One firm, Johnson & Johnson, has also done extensive testing for asbestiform particles in cosmetic-grade talc; all results to date have been negative.

3. Status of Current Studies on the Health Effects of Asbestos and Talc

Even in the case of asbestos-contamination, one must distinguish between the likely routes of exposure: inhalation, injection, and ingestion. In man, inhalation exposure to asbestos, especially when combined with cigarette smoking, has produced lung cancers. This has been well documented by Selikoff, by Hammond, and others in epidemiological studies of industrial workers (see references in attachment E). We are also aware of animal studies of asbestos inhalation which report lung tumors (attachment G).

Government agencies are sponsoring toxicological studies in animals on the effects of ingested and injected asbestos. Two of these, supported by the Environmental Protection Agency and the National Institute of Environmental Health Sciences, involve the ingestion of various kinds of asbestos particles by both hamsters and rats (attachment H). These studies were started only recently and FDA will follow their outcome closely.

Two FDA injection studies using six dose levels of small chrysotile fibers administered intravenously in both rats and mice (essentially lifetime studies) have gone to necropsy. An excess of lung tumors in the high dose mice, but not in rats, as compared to controls is suggested from preliminary, unanalyzed reports of gross necropsy findings. Histopathology and statistical analyses will require about seven months to complete. Already, however, the use of asbestos in filters used in the manufacture of parenteral drugs is restricted by FDA regulation (attachments E and F).

Finally, there are two animal inhalation studies on talc itself. The completed study was negative for carcinogenesis (attachment I). The ongoing study, contracted by FDA with Lovelace Foundation, Albuquerque, New Mexico, and initiated in 1975, has shown no positive result thus far. There are, to our knowledge, no current, direct studies of talc ingestion or intravenous injection, since the former has not yet been shown to be a hazard--even for asbestos itself--and asbestos contamination of the latter is already unacceptable.

In summary, we share your interest in the safety of talc in foods, drugs and cosmetics. The FDA is continuing its study of talc through the sponsorship of contracts for methods development and for animal studies; we also attempt to communicate with external scientific groups performing similar animal or epidemiologic studies. At present, we believe that if talc poses any risks in the products under our control, it is related to contamination by asbestos fibers. However, the FDA is prepared to take whatever prudent additional action is indicated to protect the public health, if and when results of definitive tests show that the kinds of talc in foods, drugs, or cosmetics may represent a carcinogenic hazard. FDA and other governmental agencies are well aware of the dangers of asbestos and are actively seeking the necessary information to establish enforceable limits on these mineral particles in products under our control.

We hope that these comments fully respond to your inquiry about our current efforts in this area. If you need further information, please contact Dr. Armand Casola, chairman of the FDA Asbestos Work Group. You may reach him by telephoning 301-443-6714, or by writing him at the Bureau of Drugs, Division of Anti-Infective Drug Products (HFD-140).

Sincerely yours,

Donald Kennedy
Commissioner of Food and Drugs

Enclosures (9)

Prepared by:IMAsher:HFY-313:12/11/78
Init:MNovitch:12/16/78
Edit:LBachorik:12/26/78
Init:MRosenstein:12/28/78
DKennedy:12/28/78
f/t:bjg/frf/01/05/79

cc:HF-1
HF-2
HFY-1
HFY-31
HFD-1
HFD-2
HFD-100
HFD-102(Lamar)
HFD-102(Kumkumian)
HFD-140(Casola)
HFD-400(Schaffner)
HFD-440(Eiermann)
GCF-1
HFJ-1
HFJ-5
HF-4
HFA-224

REFERENCES

Attachment A

(1) Cosmetic Talc - X2250
(2) Anthophyllite Asbestos, U.I.A.C. Std. X.2200

Attachment B

I. M. Asher and P. P. McGrath, Eds.; Electron Microscopy of Microfibers:Proceedings of the First FDA Office of Science Summer Symposium; held at the Pennsylvania State University; August 23-25, 1976.

Attachment C

Mearl F. Stanton and Contance Wrench; Mechanisms of Mesothelioma Induction with Asbestos and Fibrous Glass; J. Nat. Cancer Inst. 48:797-821, 1972.

Mearl F. Stanton, M.D.; Fiber Carcinogenesis: Is Asbestos the Only Hazard?

Mearl F. Stanton, et al., Carcinogenicity of Fibrous Glass: Pleural Response in the Rat in Relation to Fiber Dimension, J. Nat. Cancer Inst. 58:587-597, 1977.

Attachment D

Gavin Y. Hildick-Smith; The Biology of Talc; British Journal of Industrial Medicine 33:217-229, 1976.

Attachment E

Federal Register, Vol. 38, No. 188, September 28, 1973, page 27076.

Attachment F

Federal Register, Vol. 40, No. 51, March 14, 1975, page 11865.

Attachment G

B. K. J. Leong, R. J. Kociba, H. C. Pernell, R. W. Lisowe, L. W. Rampy; Induction of Pulmonary Carcinoma in Rats by Chronic Inhalation of Dust From Pulverized Asbestos Pipe Covering; Journal of Toxicology and Environmetnal Health 4:645-659, 1978.

Attachment H

John A. Moore; NIEHS Oral Asbestos Studies; Workshop on Asbestos; July 18-20, 1977, National Bureau of Standards, Gaithersburg, MD.

Attachment I

A. P. Wehner, G. M. Zwicker and W. C. Cannon, C. R. Watson and W. W. Carlton; Inhalation of Talc Baby Powder by Hamsters; Fd. Cosmet. Toxicol. 15:121-129, 1977.

A. P. Wehner, C. L. Wilkerson, W. C. Cannon, R. L. Buschbom and T. M. Tanner; Pulmonary Deposition, Translocation and Clearance of Inhaled Neutron-Activated Talc in Hamsters; Fd. Cosmet. Toxicol. 15:213-224, 1977.